Published by Elsevier Inc.

ISSN 0735-1097/03/$30.00
doi:10.1016/j.jacc.2003.09.010

EDITORIAL COMMENT

A Preferred Reperfusion Strategy for Acute Myocardial Infarction*

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The major innovations in the field of interventional cardiology in the past decade have been the introduction of stents, now with anti-inflammatory coatings, and platelet glycoprotein IIb/IIIa inhibitors. Their combined use has been validated in dedicated trials for patients undergoing elective coronary revascularization (1–3), but there has been controversy in the setting of acute myocardial infarction (MI).

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In this issue of the *Journal*, Antoniucci et al. (4) of the Abciximab and Carbostent Evaluation (ACE) trial report their primary data from the fifth randomized trial of percutaneous coronary intervention with or without abciximab, the prototypic IIb/IIIa inhibitor, for reperfusion therapy of acute MI. In this rigorous trial of 400 patients, the investigators demonstrated superiority of abciximab compared with a control arm for the primary end point of death, reinfarction, stroke, and urgent target vessel revascularization at 30 days. The salutary clinical outcomes, which were durable at six-month follow-up, are further reinforced by reduction of infarct size using sestamibi scintigraphy and improved early resolution of electrocardiographic ST-segment elevation.

The results of ACE need to be placed in context with the four previous trials: ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT) (5), Intracoronary Stenting and Antithrombotic Regimen-2 (ISAR-2) (6), Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-term Follow-up (ADMIRAL) (7), and Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) (8). In Figure 1, 30-day end points for the five trials are displayed. In pooling these data, which do not demonstrate any intertrial heterogeneity, there is an overall 46% reduction in death, reinfarction, and target vessel revascularization; a 34% reduction in death or reinfarction; and a 26% reduction in death. These results provide strong and consistent evidence of benefit for adjunctive use of abciximab with catheter-based reperfusion for MI.

Yet, until the ACE trial was performed, there had been debate in this field because of the results of the largest trial did not support the benefit of abciximab at the primary end point timing of six months. In fact, in the CADILLAC trial, there were more deaths and reinfarctions, albeit not statistically significant, among the stent-abciximab group compared with the stent control group at six months. The explanation for why this occurred, leading to particular confusion in this field, needs to be addressed. As the chairmen of the other three trials, we will attempt to shed light on this critical question.

Unlike the principal outcomes for the five trials at 30 days, which were remarkably concordant, the study designs and methodology were quite variable. In only two trials, RAPPORT and ADMIRAL, were there double-blind placebo controls. In both of these trials, abciximab study drug was encouraged to be given as early as possible after diagnosis, before the patient's entry to the cardiac catheterization laboratory. This was achieved only in 20% of the patients in RAPPORT, whereas in ADMIRAL 26% received the study drug in the emergency room or in the ambulance, and all patients had the treatment started before sheath insertion. This design, with an administration always performed before the angiogram, led to benefits of similar magnitude in high-risk versus low-risk patients (shock vs. no shock; anterior vs. other MI; young vs. elderly; diabetes vs. no diabetes). The other three trials did not allow for use of abciximab before coronary angiography, which appears to have attenuated the potential benefit of abciximab or limit its effects to the high-risk patients only. To understand the impact of early abciximab therapy, it is noteworthy that in the ADMIRAL trial there was a dramatic effect of abciximab on clot structure as analyzed in a simultaneous substudy by Collet et al. (9) and a striking 89% reduction of the six-month end point with the use of *early* abciximab. Furthermore, in that trial, the Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow before the procedure was enhanced more than three-fold among the patients with ST-segment elevation myocardial infarction (STEMI) who were randomized to receive abciximab. These results have been recently confirmed with tirofiban when administered in the emergency room before transfer for primary percutaneous coronary intervention compared with a later administration in the catheterization laboratory (10). Beyond the clinical benefits linked to an early open artery hypothesis, better flow in the culprit artery allows better visualization of length of the lesion, the side branches, the presence of thrombus, and the distal artery and may facilitate all steps of the procedure, including direct stenting, which has been

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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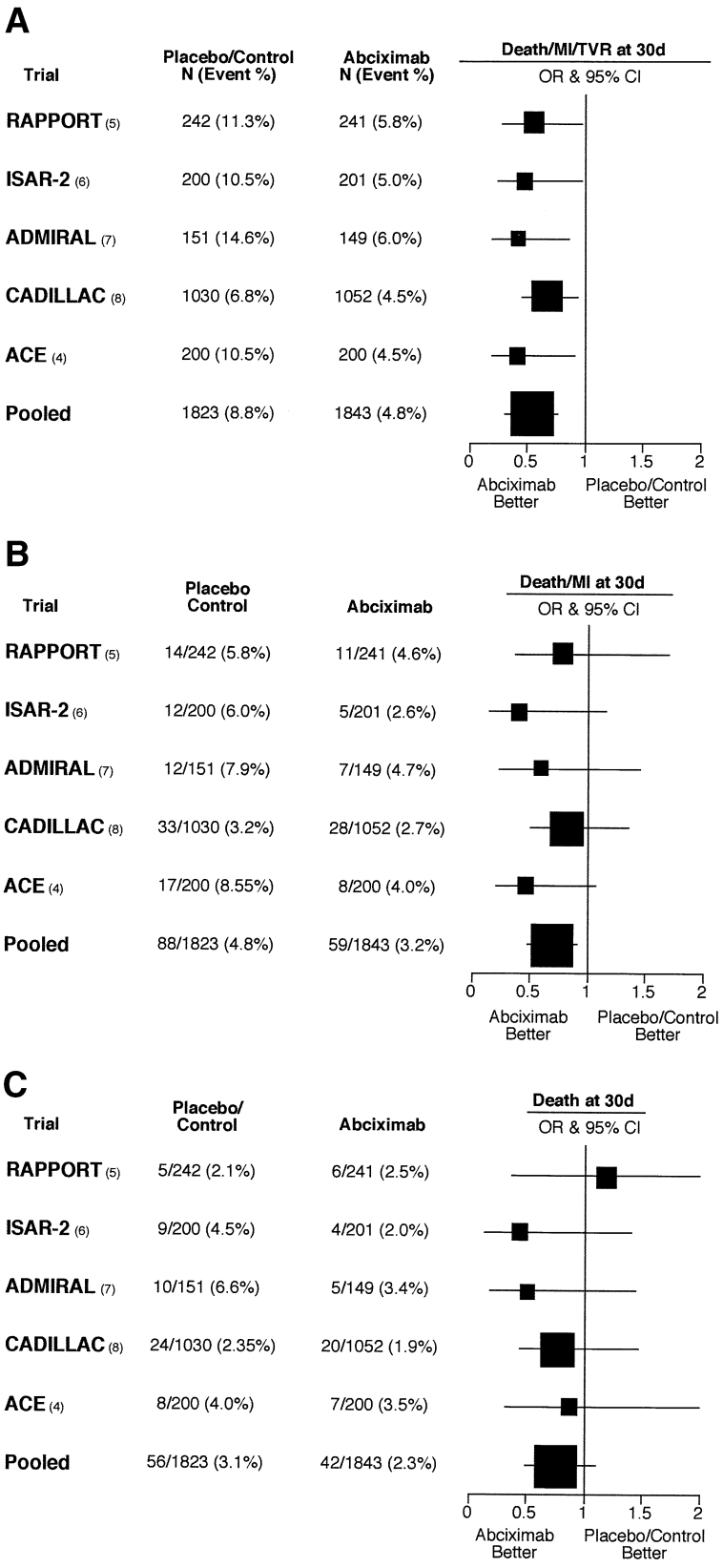

Figure 1. (A) Death, reinfarction, and target vessel revascularization (TVR) at 30 days. Two trials included stroke in the composite end point (ACE, CADILLAC), but the incidence was quite low. **(B)** Death or reinfarction at 30 days. **(C)** Death at 30 days. ACE = Abciximab and Carbostent Evaluation; ADMIRAL = Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-term Follow-up; CADILLAC = Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications; CI = confidence interval; ISAR-2 = Intracoronary Stenting and Antithrombotic Regimen-2; MI = myocardial infarction; OR = odds ratio; RAPPORT = ReoPro and Primary PTCA Organization and Randomized Trial.

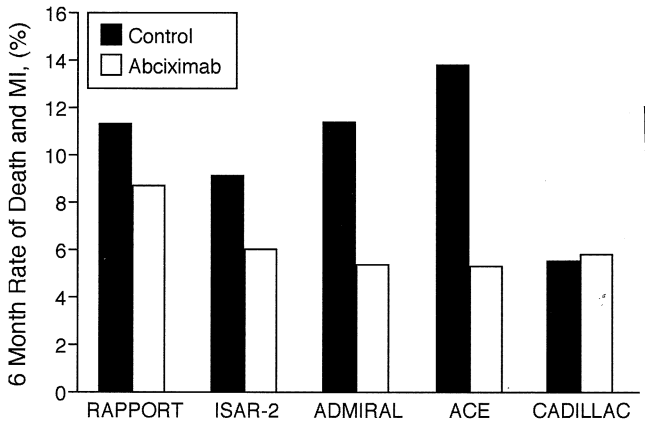

Figure 2. Rate of death and myocardial infarction (MI) at 6 months for five clinical trials of percutaneous coronary revascularization with and without abciximab. Trial abbreviations as in Figure 1.

associated with less slow flow and better ST-segment resolution (11). How much the early administration of IIb/IIIa inhibitors in STEMI patients undergoing percutaneous coronary intervention can limit thrombus extension, shorten the time of procedure, reduce the total length of stent implanted in the culprit artery, reduce distal embolization, and finally impact clinical outcome is difficult to quantify but obviously no less cost-effective compared with a later administration (12).

The entry criteria varied among the five protocols with respect to key features, such as enrollment of patients with cardiogenic shock that was supported in ISAR-2, ADMIRAL, and ACE. This is quite important because the risk of the patients varied substantially, as seen in Figure 1. Interestingly, the 30-day composite end point for CADILLAC was 6.8% in the control arm, but in each of the other four trials it exceeded 10%, reflecting the risk of the control cohorts in each trial. The low risk observed in CADILLAC was not only driven by the clinical exclusion criteria but also by the multiple angiographic exclusion criteria eliminating the anatomically difficult cases that would benefit the most from the drug. This is clearly another consequence of a strategy of late administration. It is this particular feature that likely was dominant in the explanation of why significant benefit for abciximab was not supported in the CADILLAC trial. In such a low-risk population, the opportunity for demonstrating benefit, as compared with the play of chance of clinical outcomes and type II (β) error, most likely accounts for the disparity compared with the other four smaller trials. Moreover, the definitions for end points varied among the trials, such as enzymatic criteria for diagnosis of reinfarction, and whether this end point was adjudicated by an event committee blinded to the treatment assignment. Finally, interpreting the lack of benefit of the study drug tested in a factorial design (the other objective being the comparison stent-balloon) in the only subgroup of stented patients remains questionable.

The extended follow-up data for the five trials has demonstrated an interesting pattern. In all of the trials except CADILLAC, there was support for abciximab treatment benefit for reduction of death or reinfarction at six months follow-up, and in both ADMIRAL and ACE the differences were statistically significant (Fig. 2). The preservation of the initial clinical benefit at three-year follow-up in ADMIRAL confirms further the need for this early treatment in a population representative of the risk observed in the real world (13). These findings further underscore the difficulty of interpreting durability of a treatment effect when the population exposed to the intervention being tested is one of low risk.

Beyond the five trials of percutaneous coronary revascularization with or without abciximab, there has been further validation in randomization of lytic strategies (recombinant tissue-type plasminogen activator with or without abciximab) compared with stenting with abciximab. These trials, Stent Versus Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction (STOPAMI) I and II (14,15), have both shown improved clinical outcomes and infarct size reduction for the strategy of stenting with abciximab compared with pharmacologic reperfusion therapy. Along with the recent results from randomized trials comparing transfer of patients with acute MI to specialized centers to perform catheter-based reperfusion, compared with fibrinolytic therapy (16,17), it becomes clear that angioplasty or stenting with abciximab is the preferred reperfusion strategy. Stenting has indeed been shown to be preferred over balloon angioplasty (8), but there are anatomical situations in which stenting is not logistically feasible or advisable. Furthermore, the decision whether to use abciximab should ideally be made before definition of the coronary anatomy, irrespective of whether the infarct-related artery is suitable for stenting or balloon angioplasty.

We believe that the results of the ACE trial, amalgamated with the other catheter-based reperfusion trials, provide robust evidence for the use of abciximab as a standard adjunctive therapy with catheter-based reperfusion and do not justify a different level of recommendation for the use of glycoprotein IIb/IIIa inhibitors in STEMI according to whether or not a stent is implanted (18). Considering stent plus abciximab as the gold standard for STEMI, undergoing mechanical reperfusion should impact routine practice as well as the control arms of future trials designed to test new strategies, such as full thrombolysis or combined therapy *en route* to the catheterization laboratory. The data available indicate that early use, before visualization of the coronary arteries, will be associated with the most favorable clinical outcomes. Although it may be possible to replicate the favorable findings with other IIb/IIIa inhibitors, the only available data to date have been accrued with abciximab. Unless or until there are new data available, we should regard catheter-based reperfusion with adjunctive abciximab therapy as the preferred reperfusion therapy for acute MI.

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